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## EDITORIAL

# New Insights Into Inflammatory Abdominal Aortic Aneurysms

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### Introduction

In 1972 Walker *et al.* were the first to use the term "*inflammatory abdominal aortic aneurysm*".[1] They described a distinct form of aneurysm characterised by "an unusually thick wall surrounded by extensive fibrous adhesions involving adjoining tissues and structures making the operative procedure much more difficult." These extraordinary clinicopathological findings were found in 10% of the aneurysms that they described. At that time the view of abdominal aortic aneurysms changed, and a separate clinical entity, the inflammatory aneurysm, was recognized.

Surgeons agree that the triad of thickened aneurysm wall, extensive perianeurysmal and retroperitoneal fibrosis, and dense adhesions of adjacent abdominal organs defines the inflammatory abdominal aortic aneurysm (AAA) (Fig. 1).[2] These criteria are identical to the original descriptions by Walker, who described a "thick, firm, smooth wall of the aneurysm which is shiny white in appearance." He also noted the "dense fibrosis which extends to involve adjacent structures."[1]

### Evolution of Understanding

Inflammatory AAAs were initially thought to represent distinct clinical and pathological entities different from noninflammatory aneurysms, due largely to their distinct clinical and intraoperative presentations. Their earliest descriptions were likely in the urological literature by James and DeWeerd in 1935 and 1955, respectively, and found to be associated with ureteral obstruction secondary to retroperitoneal

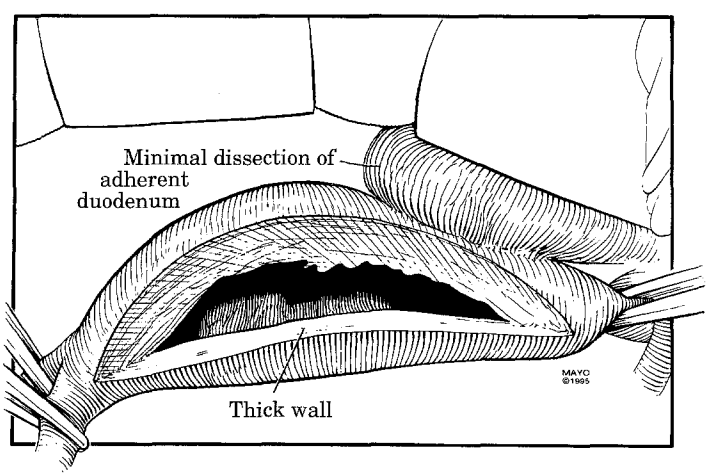


**Fig. 1.** Inflammatory, infrarenal aortic aneurysm with adherent duodenum and ureters.

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inflammation and thickening.[3,4] Walker stated that "inflammatory aneurysms are a discrete entity with significant differences from atherosclerotic aneurysms".[1] Although descriptive in nature, the original reports of inflammatory AAAs offered little regarding their aetiology.

Through histological grading of AAAs, Rose and Dent began a new way of viewing the inflammatory AAA in 1981. Not only did they speculate about the aetiology, but for the first time they suggested that inflammatory AAAs were *not* separate entities but merely the "accentuation of the chronic inflammation and fibrosis that may be observed in relation to atherosclerotic (noninflammatory) aneurysms".[5] By demonstrating that an inflammatory process was present in the aneurysm wall *in all specimens to varying degrees*, they observed that no sharp distinction existed between the usual atherosclerotic aneurysm and the inflammatory aneurysm. Furthermore, they proposed that the inflammatory aneurysm was the extreme end of an inflammatory process responsible for both the inflammatory and noninflammatory AAA.

Other surgeons subsequently demonstrated that a chronic inflammatory infiltrate occupying the adventitia exists in *both* atherosclerotic and inflammatory AAAs. Pennell and Hollier emphasised that the only difference between the noninflammatory and the inflammatory AAA is in the "intensity and extent of the inflammatory process, suggesting that they are the same disease process, differing only in the progression of the inflammation".[6] In a similar fashion, Sterpetti has described "a gradual passage, in terms of inflammatory response, from ordinary atherosclerotic to inflammatory response."[7]

Emerging data support this theory and suggest a primary inflammatory response to an unknown antigen present within the aortic wall. This response is characterised by aortic-wall infiltrating macrophages, T-lymphocytes, and B-lymphocytes that activate proteolytic activity through the production of cytokines.[8–11] This proteolytic activity leads to increased turnover in the matrix proteins, elastin, and collagen. Subsequent loss of aortic wall integrity and tensile strength occur as an aneurysm forms. This inflammatory process is accentuated in certain persons with environmental risks (e.g. smoking) or a genetic predisposition. The extreme end of the inflammatory spectrum is reached and results in an inflammatory AAA at a relatively younger age.

Investigations are now focused on identifying the inducing agent, endogenous or exogenous, of this immune response. Efforts to isolate the antigen *directly* from aneurysmal tissue have yielded mixed results. Breakdown products of elastin and/or red blood cells, as well as oxidized low density lipoproteins, have been suggested as *endogenous* antigens. In addition, studies by Tilson using immunoglobulin and amino acid sequencing techniques provide evidence that an *endogenous* autoantigen exists in aneurysmal disease, which is similar to a microfibril-associated glycoprotein, and raises the question of autoimmunity as an important mechanism in the pathogenesis of aneurysms.[12,13]

In other attempts to directly isolate the antigen directly from aortic tissue, Tanaka *et al.* published evidence that the human herpes virus may play a role as an *exogenous* antigen in the pathogenesis of aortic diseases.[14,15] Using DNA polymerase chain reactions, they demonstrated that either the herpes simplex virus or cytomegalovirus was present more frequently in the wall of aneurysms than in normal aortic wall. In addition, these viruses were more prevalent in inflammatory than noninflammatory AAAs. They hypothesised that the replicating infections of the cytomegalovirus may cause the formation of inflammatory aneurysms.

Our recent investigations have focused on *indirect* approaches to characterising a possible antigen related to the pathogenesis of inflammatory AAAs. While effecting an immune response, an antigen by nature leaves a fingerprint of its basic amino acid structure. This fingerprint can be viewed from three different vantage points and exists as: (i) the selective interaction with specific class II HLA molecules, (ii) the preferential activation of certain inflammatory cells and pathways, and (iii) the selective interaction with certain T cell receptors. Our studies have focused on characterising the first of these antigen fingerprints, its interaction with specific class II HLA molecules.

Through HLA typing of patients with inflammatory AAAs, we have demonstrated that patients with inflammatory AAAs possess a genetic risk determinant which can be mapped to the HLA region.[16] Specifically, we demonstrated that patients with inflammatory AAAs preferentially express a unique configuration and electrical charge of an antigen binding pocket of the HLA-DR molecule, which may represent a portion of the fingerprint left by the responsible antigen. Characterisation of this fingerprint may allow for predictions regarding antigenic epitopes and charged composition.

Also of importance is that our work with inflammatory AAAs has raised the question of tobacco as a significant environmental promoter of this disease process. We have previously demonstrated that a greater percentage of patients with inflammatory

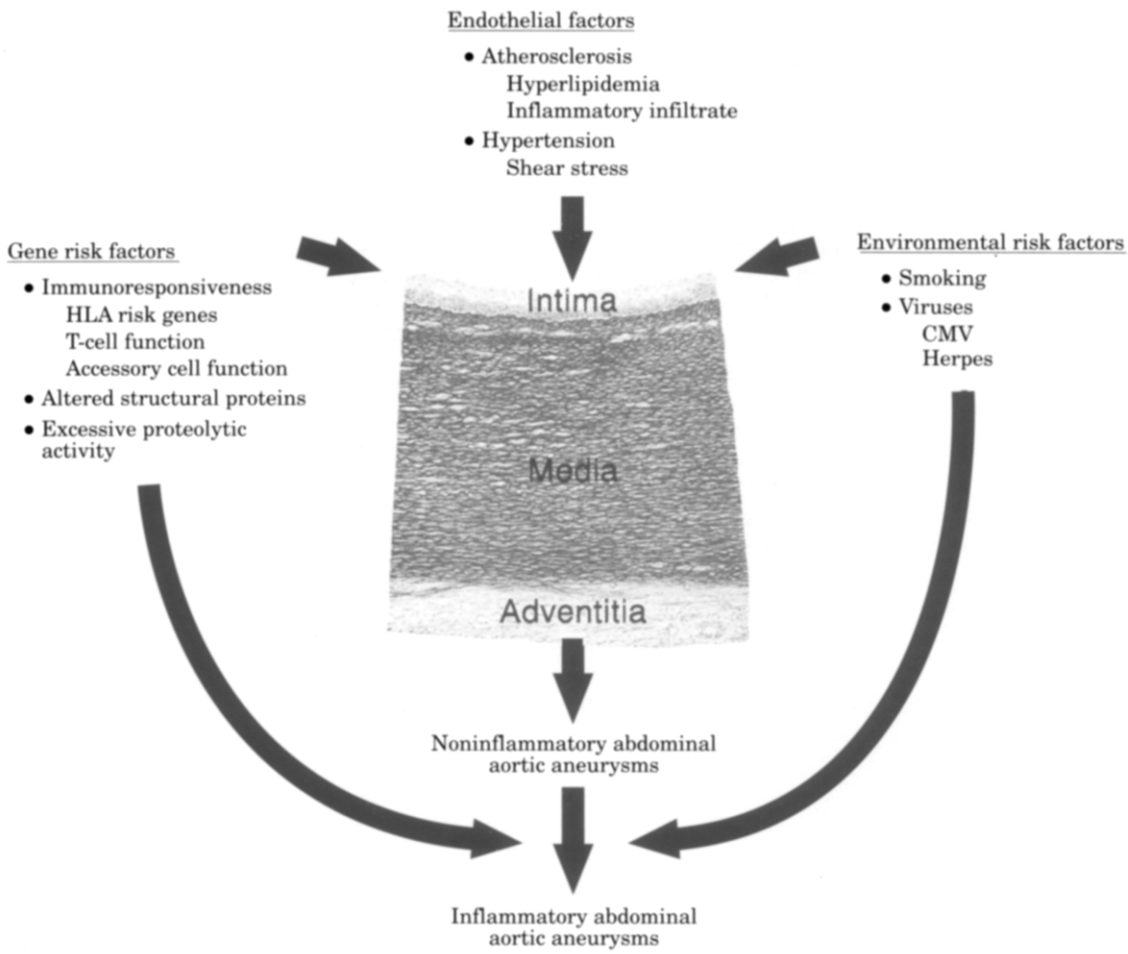


**Fig. 2.** A schematic representing the multifactorial pathogenesis of aneurysm development. The three catagories of risk factors, genetic, endothelial, and environmental, may also play a role in the progression from the noninflammatory aneurysm to the inflammatory abdominal aortic aneurysm.

AAAs were current smokers than patients with non-inflammatory AAAs,[17] and a subgroup of patients in our recent study appeared to use tobacco more frequently and manifest a more aggressive inflammatory response.[16]

Although the understanding of inflammatory AAAs has evolved much in the 25 years since they were first described by Walker, their aetiology remains unknown and is likely multifactorial (Fig. 2). A combination of environmental/antigenic, endothelial and genetic factors likely act upon the vessel wall and cause aneurysm formation. These same factors *may* be responsible, in certain persons, for the development of the inflammatory AAA. Further studies to better characterise these factors and the molecular and cellular mechanisms at play in the pathogenesis of inflammatory AAAs are required.

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